Does addition of glucocorticoids to the initial therapy influence the later course of the disease in patients with early RA? Results from the Swiss prospective observational registry (SCQM)

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Abstract: The main goal of this study was to analyse whether initial addition of glucocorticoid to DMARD therapy influences the long-term course of the disease in patients with early rheumatoid arthritis. All patients from the Swiss RA cohort SCQM with recent-onset arthritis (disease duration 1 year) were analysed. The exposure of interest was the use of glucocorticoids (GCs) at baseline. As primary outcome, we considered clinical and radiographic disease progression, assessed by the disease activity (disease activity score, DAS-28), function (health assessment questionnaire disability index, HAQ-DI) and structural joint damage (Ratingen erosion score). The baseline disease characteristics were compared using standard descriptive statistics. The effects of initial GC use on disease progression during follow-up were estimated using linear mixed models with random slope and random intercept, adjusted for potential confounders. In total, 592 patients with early disease were available, with 4.3 years of follow-up (average). Of these, 363 were initially treated with glucocorticoids (GC patients) and 228 were not (no-GC patients). DAS-28 (4.6 vs. 4.3, $p = 0.01$) and the HAQ-DI (0.94 vs. 0.82, $p = 0.01$) were higher at baseline in GC patients, while other prognostic factors were balanced at baseline. Neither the change of DAS-28, of HAQ-DI nor of the development of joint erosions differed between the two groups during follow-up. Escalation of treatment employing biologics was documented in 18.0% of the no-GC patients and 27.3% of the GC patients ($p < 0.01$). In this cohort, patients with early RA initially treated with GCs had higher measures of disease activity at baseline in comparison to no-GC patients. Despite a similar course of the disease in GC versus non-GC patients, the higher escalation rate to biologic agents in GC patients may reflect a disease less responsive to therapy in these patients. These data suggest that GC use as part of the initial therapeutic strategy in early RA may prevent a more severe course of the disease in patients with higher clinical disease measures at the start of therapy.

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Running title: *Clinical and radiographic progression as a function of the initial use of glucocorticoids*

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Key message: The use of GC in early arthritis may compensate unfavourable prognostic factors

Contributorship:

RM: setup of the study, interpretation of data, writing of the manuscript
NR: interpretation of data, writing of the manuscript
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Disclosure:

The authors have nothing to disclose that directly or indirectly might affect, or be perceived to affect, the conduct or reporting of the work they have submitted.

Competing interests:

none

Abstract:

Background: The main goal of this study was to analyse whether initial addition of glucocorticoid to DMARD therapy influences the long-term course of the disease in patients with early rheumatoid arthritis.

Method: All patients from the Swiss RA cohort SCQM with recent onset arthritis (disease duration ≤1 year) were analysed. The exposure of interest was the use of GCs at baseline. As primary outcome we considered clinical and radiographic disease progression, assessed by the disease activity (DAS 28), function (HAQ DI) and structural joint damage (Ratingen erosion score). The baseline disease characteristics were compared using standard descriptive statistics. The effects of initial GC use on disease progression during follow up was estimated using linear mixed models with random slope and random intercept, adjusted for potential confounders.

Results: In total, 592 patients with early disease were available, with 4.3 years of follow-up (average). Of these, 363 were initially treated with glucocorticoids (GC patients) and 228 were not (no-GC patients). DAS-28 (4.6 vs. 4.3, $p = 0.01$) and the HAQ-DI (0.94 vs. 0.82, $p = 0.01$) were higher at baseline in GC patients, while other prognostic factors were balanced at baseline. Neither the change of DAS-28, of HAQ-DI, nor of the development of joint erosions differed between the two groups during follow up. Escalation of treatment employing biologics was documented in 18.0% of the no-GC patients and 27.3% of the GC patients ($p < 0.01$).

Conclusion:

In this cohort, patients with early RA initially treated with GCs had higher measures of disease activity at baseline in comparison to no-GC patients. Despite a similar course of the disease in GC versus non-GC patients, the higher escalation rate to biologic agents in GC patients may reflect a disease less responsive to therapy in these patients.

These data suggest that GC use as part of the initial therapeutic strategy in early RA may prevent a more severe course of the disease in patients with higher clinical disease measures at the start of therapy.

Key words: glucocorticoids, rheumatoid arthritis, disease progression, early disease

Significance & Innovation:

- GC use may have a beneficial role in patients with unfavourable prognostic factors.
  - Patients with initial GC treatment had more unfavourable prognostic factors than those without.
  - Early RA patients with and without initial GC use demonstrated similar clinical and radiographic development during follow-up.
- In our opinion, in the absence of contraindications, GCs should always be considered as bridging therapy in early disease, and used, in particular, if unfavourable prognostic factors are present.

Introduction:

Glucocorticoids (GC) have anti-inflammatory and disease-modifying properties in RA patients (1-3). GC treatment added to DMARD therapy is successful at low (<10 mg/day) (4-6) and at higher doses (7, 8). Higher doses of GCs lead to a more rapid short-term clinical improvement in comparison to patients not treated with GCs at all (7). In the COBRA-light study a reduced glucocorticoid dose was equally effective as higher GC doses employed in the classical COBRA regimen (9).

Whether the significantly better outcomes in clinical trials using combinations of synthetic DMARDs plus GCs versus DMARD monotherapy might be at least in part be due to the GC component (6-8) is under discussion. This hypothesis is supported by studies showing that adding GC to DMARD monotherapy(4, 5) is beneficial.

It is well known that long or even intermediate-term use of GCs can lead to adverse events (10). The EULAR task force, therefore, recommends that GCs should be tapered as rapidly as possible (11).

The primary objective of this study was to analyze whether initial corticosteroid therapy influences the course of early disease in RA patients. A secondary objective of this study was to compare baseline characteristics of early arthritis patients with or without initial GC use, possibly explaining the rheumatologist's decision to add GCs.

METHODS:

Study population and design

The Swiss Clinical Quality Management in rheumatoid arthritis (SCQM) is a RA national cohort study performed by office or hospital based rheumatologists, which has been described in detail elsewhere (12, 13). SCQM has obtained a Swiss-wide ethical approval to collect patient data and a broad consent to perform clinical research related to its aims. In this study, we restricted our analysis to patients with early RA. The analysis includes data collected between January 1998 and November 2011. Inclusion criteria for the analysis were a diagnosis of RA by a rheumatologist, and early disease, as defined as less than 367 days from the first symptoms (as reported by the patient). Patients treated with GCs, synthetic or biological DMARDs for more than 31 days before the first visit were excluded from the analysis. Exclusion criteria were missing 28 joint counts at baseline or the absence of follow-up visits, as published before (14, 15).

Exposure of interest

The primary objective of the study was to analyse whether initial GC therapy influences the course of the disease in early RA patients.

Outcome parameters

The primary endpoint was the change of DAS-28 scores. Secondary endpoints were changes in radiographic joint damage and patient centred outcomes. The patient centred outcome was assessed using the Stanford Health Assessment Questionnaire (HAQ DI) (16). Radiographic damage was analyzed on serial radiographs according to the number and the size of bone erosions. Erosions were measured prospectively using a validated scoring system (Ratingen score) (17), based on the amount of joint-surface destruction for each joint. The inter-observer agreement and test-retest reliability were high, as published (17).

To predict, at baseline, the GC use after 2 years, as a secondary endpoint, all RA patients were separated into two groups depending on the documented GC use after two years (defined as long-term use of GCs). The two groups were re-analyzed for differences in baseline characteristics.

Statistical analysis

The baseline disease characteristics of patients in the two groups were compared using standard descriptive statistics. Continuous variables were compared using a Student´s T-test, categorical variables with X^2 test. Curves showing changes in DAS-28 and HAQ DI scores over time were created using loess smoothing of the raw data. The effect of initial GC use on DAS-28 and HAQ DI scores was estimated using linear mixed models with random slope and random intercept, and adjusted for various baseline factors in a univariate fashion, as well as in a multivariate fashion considering baseline DAS-28 (or HAQ DI), Ratingen score and ESR. We also examined whether GC initiation was influenced by baseline parameters, ACR/EULAR classification score, rheumatoid factor, DAS-28, ACPA, ESR, age, gender or calendar year of inclusion, in a propensity score analysis using multiple logistic regression. A propensity score was then computed as the predicted log-odds of receiving GCs at baseline, and included as a univariate predictor in the linear mixed models described above. All statistical analyses were 2-sided at the 0.05 significance level. The analyses were performed using Graph pad Prism 5 software and the lme4 package in R.

Ethics approval

Ethics approval for the collection of patient data for the SCQM Cohort was given by the regional review boards. Informed consent was obtained from all patients before inclusion in the SCQM Cohort.

RESULTS:

Patients:

Of the 9´627 patients in the database, 756 patients had early RA with a symptom duration of less than 367 days. 609 patients of these had at least one follow-up in the database, and 592 patients in the database had valid 28 joint counts. The median follow-up for these 592 patients was 44 months (range 0 – 178), representing a total of 3'845 visits.

Baseline demographical data:

Patients were categorized into two groups: patients treated with GCs (GC patients, n=363) and not treated with GC (n=228, no-GC patients) at baseline. Analysis of the demographical data revealed no significant differences in age, gender, disease duration, and time of follow up between the two patient groups, as shown in Table 1. In 2 patients new treatment was initiated within the period of 31 days prior to baseline. Exclusion of these patients from did not influence data analysis (not shown). Disease activity was higher at the inclusion visit in GC patients. In detail, mean DAS-28 was 4.6 in GC patients vs. 4.3 in no-GC patients ($p = 0.011$). Similarly, the ESR was also higher in GC patients (mean 30.5 vs. 24.3mm/h, resp., $p = 0.0013$), whereas CRP (mean 23.7 GC vs. 15.8 no GC, $p = 0.13$), swollen (7.9 vs. 7.1, $p = 0.09$) and tender (8.0 vs. 7.6, $p = 0.48$) joint count, and erosion scores at disease onset showed no statistically significant differences. ACPA and rheumatoid factors also did not differ between the two patient groups. The average HAQ DI was higher in GC (0.94) than in no-GC patients (0.82, $p = 0.0122$, Table 1).

The average GC dose in the GC patients was 14.0mg/d (±9.28)at baseline (median 10mg/d). The range was from1.25mg/d to 60mg/d (Figure 1).

Clinical and radiographic progression:

Disease activity, patient reported outcome, and development of joint erosions were similar in both patient groups during follow up, as demonstrated by DAS-28, HAQ-DI, and erosion scores (Figure 2). The time of follow up between the two patient groups did not differ (mean 171.2 months GC vs. 186.9 months no-GC, $p = 0.0529$).

To find out whether GCs were preferentially started in more severe cases of RA, we analyzed if GC initiation was associated with the baseline parameters (rheumatoid factor, DAS-28, ACPA, ESR, age, gender and calendar year) in a propensity score analysis using logistic regression (not shown). After adjusting for this propensity score, no statistically

significant difference in clinical activity (difference in DAS-28 0.04 on average, p = 0.67) or radiographic disease progression (erosion score 0.75 higher in GC patients, p = 0.29) was observed in patients with and without the use of GCs. The same was true for the patient oriented outcome (HAQ-DI 0.03 higher in GC patients, p = 0.47). The results were similar when using a propensity score from the best-fit model, which included only age and baseline ESR.

Drug survival of initial GCs and new initiation of GCs during follow up:

The drug survival of GCs after start at baseline was analyzed. GC treatment was stopped in 301 patients during follow up, after a median of 680 days. In parallel, GC treatment was initiated in 48 of the initial no-GC patients after an average of 662 days (Figure 3A). Thus, GC treatment was continued in 47.2% of the initial GC patients and started in 21.9% after 2 years of follow up of the initial no-GC patients (not statistically significant).

Conventional synthetic DMARD treatment:

Treatment with conventional synthetic DMARDs was initiated preferentially with methotrexate (MTX) in both treatment groups. MTX was a part of the initial therapeutic strategy in 75.5% of the GC patients and 66.9% of the no-GC patients (X^2 test: 4.492,1, p = 0.03, table 2). The average initial MTX doses were 14.4 and 14.1mg/week in the GC and no-GC patients respectively (data not shown). In parallel, the first therapeutic modification (independent of whether the MTX dose was modified in patients already treated with MTX or whether MTX was initiated) was more frequent in GC patients (23.4% in GC vs. 4.7% in no-GC patients, X^2 test: 38.32,1, p < 0.0001). There were no significant differences comparing GC and no-GC patients for the use of sulfasalazine, anti-malarials, and leflunomide (data not shown).

Escalation to biologics:

Escalation of treatment with biologic agents occurred in 18.0% of the no-GC patients after 909 days on average and in 27.3% of the GC patients after 754 days (X^2 Test for the number of patients requiring biologics: 6.96, p = 0.0097, time to first biologic p = 0.31, Figure 3b).

Co-morbidities:

Analysis of the number and kind of co-morbidities in our cohort of early RA patients did not reveal differences between the two patient groups, neither at baseline, nor during follow up (table 3).

Predictors for GC use after 2 years

To explore which baseline parameters were associated with long-term GC treatment, we examined patients still on GC after 2 years (table 4). Patients with long-term GC use over 2 years had an increased HAQ DI of 1.05 at baseline, as compared to 0.86 in those not treated with GCs after 2 years ($p = 0.005$), but no other differences were found for the different demographical, serological, and parameters indicative of disease activity or joint destruction.

Discussion:

In this study, we analyzed the effect of initial GC treatment as an adjunct to DMARD therapy in a cohort of 592 RA patients with early disease. Patients treated with GCs had higher objective and subjective disease activity at the first visit, as measured by the DAS-28 and HAQ DI, respectively. These differences evened out during follow up.

These results may help to shed light on two frequently debated questions:

- Is the decision for initial treatment with GCs triggered by unfavourable prognostic factors?
- Is GC use from first clinical visit onwards in early RA necessary to modify the further course of the disease?

Is the decision for initial treatment with GCs triggered by unfavourable prognostic factors?

In our study, disease activity (ESR, DAS-28) was higher and functional limitations (HAQ DI) were more pronounced in patients initially treated with GCs than in those who were not. The most likely explanation is that rheumatologists tended to add concomitant GC preferentially to their patients with more severe RA, which is corroborated by the fact that these patients also received more frequently biologic anti-rheumatic agents during follow-up than non-GC users.

It is well known that long-term GC treatment is associated with many adverse events. As a consequence, rheumatologists try to taper and eventually stop GCs. The reasons for maintaining GC treatment for an extended period of time should be well founded and GCs should only be used because of a therapeutic necessity in the individual patient. In our study, 20 – 50% of the patients were still treated with GCs after two years (Figure 3A). The HAQ DI at baseline was the only parameter significantly higher in patients on GCs after two years. The patient's individual perception of disease-associated limitations affecting functionality in daily life, thus, correlated with the use for GCs after two years.

Another explanation for initial use of GCs could be the application of predefined therapeutic concepts including the use of GCs in all early RA cases by individual rheumatologists or centers. However, we could not demonstrate an association between the initial use of GCs and individual rheumatologists or centers involved (data not shown), suggesting that GC use was no related to a strong physician bias as in a natural study.

Is the GC use from first clinical visit onwards in early RA necessary to modify the further course of the disease?

In view of the loss of the initial differences in disease activity during follow up, our data suggest -at first sight - that the initial use of GCs does not improve long-term results.

No differences between patients initially treated or not with GCs in radiographic progression, DAS-28 or HAQ DI could be found. However, biologic agents were more frequently initiated during follow up in GC- than in no-GC patients, most probably reflecting an initial clinical disease state less responsive to therapy in these patients. GC may only be necessary in patients with higher baseline DAS and HAQ-DI scores.

A considerable number of clinical studies (18) has demonstrated that more aggressive treatment may lead to better results (19). Increased baseline parameters such as ESR, high joint counts as part of the DAS-28 and HAQ DI are known to have a negative influence on the course of RA (20, 21) . These parameters were higher in the GC group (22) of our cohort, indicating a potential for more aggressive disease. Considering the equal course of disease in the two patient groups, GCs may actually have prevented a more severe course of the disease. In the EULAR guidelines recommend that “low-dose glucocorticoids” should ideally be considered ”as part of the initial treatment strategy” since addition of GCs to DMARD therapy as “bridging therapy” has been shown to have a similar effect as the addition of a TNF antagonist to MTX (11, 23-25). In view of the multitude of parameters involved, data derived from clinical cohorts are never unequivocal. Our analysis, however, may support the use of GC in early RA in patients with higher clinical disease measures such as higher DAS-28, ESR and HAQ-DI (high DAS-28, ESR, and HAQ-DI, (20, 21)). This conclusion is similar to the statement in the EULAR guidelines in Phase II for the therapeutic decision after the first DMARD has failed (11). These recommendations propose a second synthetical DMARDs in patients with favourable and a first biologic agents in those with unfavourable prognostic factors.

Health economic considerations:

The percentage of 27% GC- and 15% no-GC-patients requiring a step up of therapy to a biologic agent appeared rather low. A possible reason for this may have been the relatively early recruitment period of January 1998 and November 2011(median May 15th 2005) in our cohort. However, this rate is comparable to others published by Fiehn et al. in Germany for the time period 1997 – 2005 or, more recently, for the Dutch tREACH cohort (23, 26). Considering yearly costs of CHF 21´232,90 for a biologic agent (e.g. Adalimumab, Switzerland OTC price) and CHF 119,-- for 10 mg prednisolone (e.g. Spiricort, Switzerland OTC price), reduction of biologic agents by e.g. 5% would be equivalent to overall savings of CHF 94´265 (in 100 patients). Or, in other words, the costs would be equivalent if 178 early RA patients are treated continuously with prednisolone over one year and in one patient out of these 178 therapy is not escalated a biologic agent. These considerations are, as a matter of course, purely economic and do not take into account costs caused by therapy related side effects of either corticosteroids or biologics.

Limitation:

GCs are frequently associated with AEs. Assessment of AEs is certainly an issue for the analysis of cohort data. We have analysed the adverse event rate in both groups and found no differences between the two groups (data not shown). The relative risk for a comorbidity was 1.12 comparing GC and no GC patients. The leads to a number needed to harm (NNH) of 1960.1. However, the rate of AEs was very low and we think that underreporting of AEs is a major bias to this analysis.

The initial glucocorticoid doses employed in the GC patients varied from 1.25 to 60mg/d at onset of treatment. The improved effect of higher initial GC doses has been reviewed by Laan et al. (27). However, it cannot be derived from the database whether the physicians coded the GC dose initiated or, rather, the dose reached after initial tapering. Therefore, no conclusions can be drawn from our data on the initial GC dose used and its effect on the course of the disease.

Summary and conclusions:

Patients with initial GC treatment had more unfavourable prognostic factors than those without, implying a more aggressive evolution of their disease. However, early RA patients with and without initial GC use demonstrated similar clinical and radiographic evolution, suggesting that initial GC use may have had a beneficial role in these patients with unfavourable prognostic factors. In our opinion, in the absence of contraindications, GCs should be considered as bridging therapy in early disease in particular, if prognostic factors of severe disease are present.

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Tables, Figure legends:

Table 1: Patient baseline characteristics

GC use initiated at baseline	Present	Not present	P value
Number	363	228	-
Age (years, mean ± SD)	55.1 ± 14.8	51.3 ± 15.2	0.034
Gender (f/m)	257/106	172/56	0.214
Follow-up (months, mean ± SD)	51.4 ± 37.2	50.6 ± 39.1	0.80
Symptom durations (days, mean ± SD)	171.2 ± 98.5	186.9 ± 94.5	0.0529
SJC at onset (mean ± SD)	7.9 ±6.0	7.1 ± 5.9	0.088
TJC at onset (mean ± SD)	8.0 ± 6.8	7.6 ±6.6	0.48
DAS-28 at onset (mean ± SD)	4.6 ± 1.6	4.3 ± 1.6	0.011
RF pos. at onset (n, %*)	231, 63.6%	157, 68.9%	0.19
CCP pos. at onset (n, %*)	85, 62.0%	66, 65.3%	0.60
ESR at onset, mm/h (mean ± SD)	30.5 ± 25.3	24.3 ± 20.4	0.0013
CRP at onset, mg/l (mean ± SD)	23.7 ± 12.1	15.8 ± 11.5	0.13
Ratingen score at onset	8.9 ± 9.6	7.1 ± 8.4	0.0614
HAQ-DI at onset	0.94 ± 0.71	0.82 ± 0.65	0.0122
Initial GC dose (av. mg ± SD, range, median)	14.1 ± 9.8, 2.5-50, 10	0 ± 0, 0	-

f: female
GC: Glucocortioid
m: male
TJC: Tender joint count
SJC: Swollen joint count
RF: rheumatoid factor
CCP: antibodies to cyclic citrullinated peptides
CRP: C reactive protein
n.a. not applicable
LORA: Late onset rheumatoid arthritis (>60a)
YORA: Young onset rheumatoid arthritis (<60a)

- Calculated on patients with available data

Table 2: Percentage of patients on certain drug therapy (%)

		MTX	SSZ	Lef	HCQ
Initial therapeutic strategy	No-GC	66.9	10.5	6.8	6.0
	GC	75.5	12.0	4.6	9.8
1st modification of initial therapy	No-GC	4.7	6.0	5.5	6.9
	GC	23.4	7.2	11.0	6.3
2nd modification of initial therapy	No-GC	6.1	4.4	6.1	2.2
	GC	9.2	4.4	4.1	3.6
3rd modification of initial therapy	No-GC	5.3	0	1.8	1.3
	GC	4.4	0.6	5.2	1.9
4th modification of initial therapy	No-GC	1.3	0.4	1.3	0.9
	GC	1.3	0.6	2.2	0.8

No-GC: Patients initially treated with glucocorticoids
GC: Patients initially treated without glucocorticoids
MTX: Methotrexate
SSZ: Sulfasalazine
Lef: Leflunomide
HCQ: Hydroxychloroquine

Table 3: Comorbidities:

	GC	no-GC
Total	n = 92	n = 51
Allergical	n = 11	n = 5
Cardiological	n = 5	n = 2
Dermatological	n = 18	n = 7
Gastrointestinal	n = 24	n = 16
General	n = 2	n = 4
Hematological	n = 1	n = 3
Hepatical	n = 1	-
Ears, nose, through	n = 2	n = 2
Infectious	n = 8	n = 4
Musculosceletal	n = 2	-
Neoplasia	n = 1	n = 3
Nephrological	n =1	-
Nephrological	-	n = 1
Neuropsychiatric	n = 8	n = 1
Not defined	n = 3	n = 1
Ophthalmologic	n = 1	-
Pulmonary	n = 4	n = 2

Table 4: Patient characteristics at baseline depending on the GC use after two years

GC used after 2 years	still on GC	no-GC	P value
Number	153	439	-
Age (years, mean ± SD)	54.6 ± 15.1	53.3 ± 15.1	0.37
Gender (f/m)	112/41	317/122	0.06
Follow-up (months, mean ± SD)	63.7 ± 36.5	46.8 ± 37.5	<0.0001
Disease durations (days, mean ± SD)	181.2 ± 99.7	175.8 ± 96.4	0.56
SJC at onset (mean ± SD)	7.8 ± 6.1	7.5 ± 5.9	0.66
TJC at onset (mean ± SD)	8.3 ± 7.2	7.7 ± 6.5	0.32
DAS-28 at onset (mean ± SD)	4.6 ± 1.6	4.5 ± 1.5	0.30
RF pos. at onset (n, %*)	107, 69.9 %	281, 64.0%	0.18
CCP pos. at onset (n, %*)	35, 62.5%	116, 63.4%	0.90
ESR at onset, mm/h (mean ± SD)	31.2 ± 24.8	27.1 ± 23.3	0.08
CRP at onset, mg/l (mean ± SD)	27.0 ± 9.1	19.3 ± 12.6	0.45
Ratingen score at onset	8.1 ± 8.6	8.4 ± 8.6	0.74
HAQ-DI at onset	1.05 ± 0.73	0.86 ± 0.67	0.005

f: female
GC: Glucocorticoids
m: male
TJC: Tender joint count
SJC: Swollen joint count
RF: rheumatoid factor
CCP: antibodies to cyclic citrullinated peptides
CRP: C reactive protein
n.a. not applicable
LORA: Late onset rheumatoid arthritis (>60a)
YORA: Young onset rheumatoid arthritis (<60a)
* Calculated on patients with available data

Figure 1: Average GC doses. The average GC doses are demonstrated depending on the number of patients initiated on the respected dose

Figure 2: DAS-28, HAQ scores and radiographic progression over time. Patient groups were analyzed separately for initial GC (dotted grey line, GC patients) and no initial GC use (solid black line, no-GC patients). Loess smoothed time-courses of DAS-28 (A), Ratingen (B), and (C) HAQ DI scores are depicted per group over 60 months of follow-up.

Figure 3. Time to stop/start glucocorticoids and time to start the first biologic DMARD. (A) The time to stop glucocorticoids (black line) and the time to start glucocorticoids (grey line) in patients initiated with GC (black line) and patients initiated without GCs (grey line). The time was assessed in days from the first documented therapy for RA in our cohort within the SCQM registry. Patients are presented as percentage of either group. (B) The time to initiation of the first biologic DMARD was shown in days after the first visit in patients initiated without glucocorticoids (black line) and patients initiated without GCs (grey line). Data was shown as percentage per patient group. The time to biologic is demonstrated as days after the first visit.

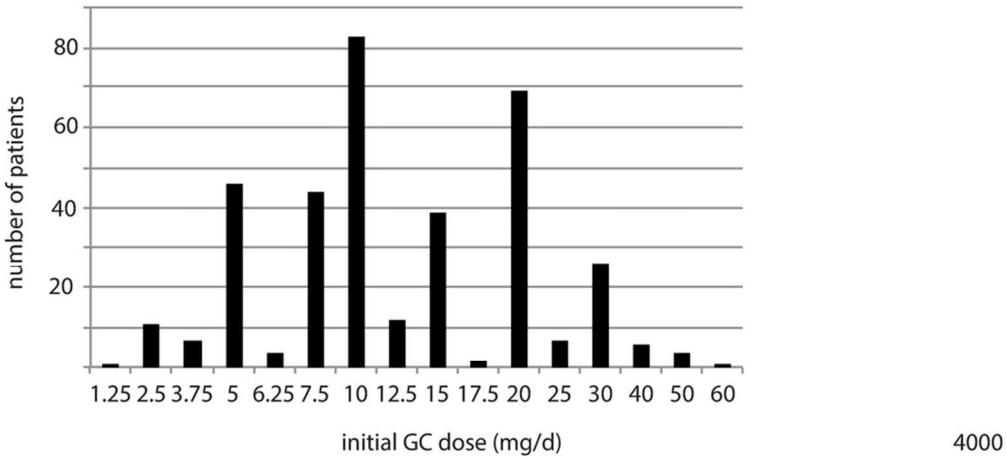

Figure 1: Average GC doses. The average GC doses are demonstrated depending on the number of patients initiated on the respected dose

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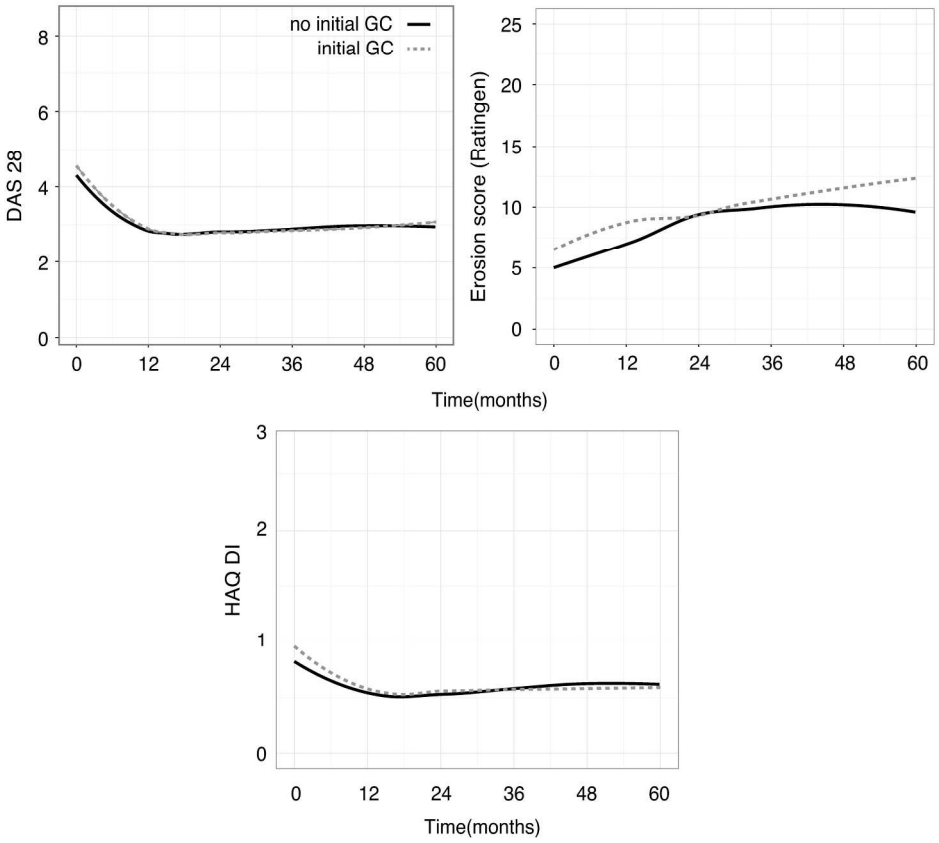

Figure 2: DAS-28, HAQ scores and radiographic progression over time. Patient groups were analyzed separately for initial GC (dotted grey line, GC patients) and no initial GC use (solid black line, no-GC patients). Loess smoothed time-courses of DAS-28 (A), Ratingen (B), and (C) HAQ DI scores are depicted per group over 60 months of follow-up.

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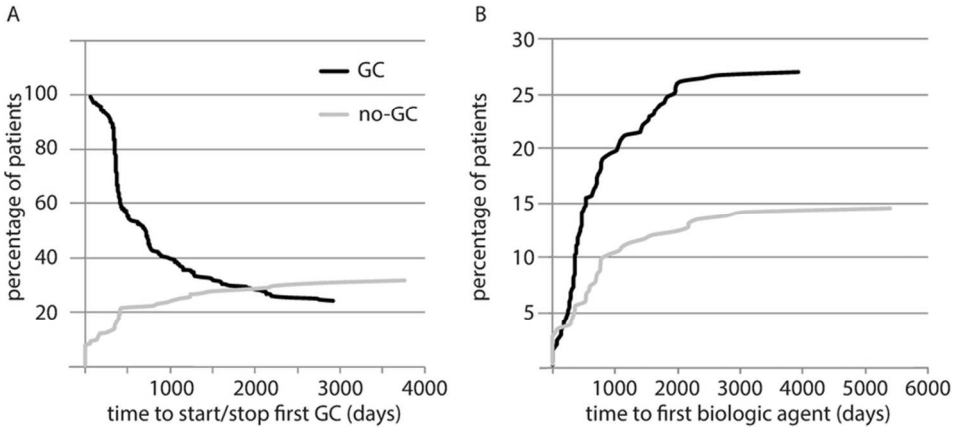

Figure 3. Time to stop/start glucocorticoids and time to start the first biologic DMARD. (A) The time to stop glucocorticoids (black line) and the time to start glucocorticoids (grey line) in patients initiated with GC (black line) and patients initiated without GCs (grey line). The time was assessed in days from the first documented therapy for RA in our cohort within the SCQM registry. Patients are presented as percentage of either group. (B) The time to initiation of the first biologic DMARD was shown in days after the first visit in patients initiated without glucocorticoids (black line) and patients initiated without GCs (grey line). Data was shown as percentage per patient group. The time to biologic is demonstrated as days after the first visit.

80x34mm (300 x 300 DPI)

Does addition of glucocortiocids to the initial therapy influence the later course of the disease in patients with early RA? Results from the Swiss prospective observational registry (SCQM)

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Running title: *Clinical and radiographic progression as a function of the initial use of glucocorticoids*

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Key message: The use of GC in early arthritis may compensate unfavourable prognostic factors

Contributorship:

RM: setup of the study, interpretation of data, writing of the manuscript
NR: interpretation of data, writing of the manuscript
TK: interpretation of data, writing of the manuscript

AF: interpretation of data, writing of the manuscript
SH: interpretation of data, writing of the manuscript
HS: interpretation of data, writing of the manuscript
MSch: interpretation of data, writing of the manuscript
MSp: interpretation of data, writing of the manuscript
JK: setup of the study, interpretation of data, writing of the manuscript

All authors read and approved the manuscript

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Disclosure:

The authors have nothing to disclose that directly or indirectly might affect, or be perceived to affect, the conduct or reporting of the work they have submitted.

Competing interests:

none

Abstract:

Background: The main goal of this study was to analyse whether initial addition of glucocorticoid to DMARD therapy influences the long-term course of the disease in patients with early rheumatoid arthritis.

Method: All patients from the Swiss RA cohort SCQM with recent onset arthritis (disease duration ≤1 year) were analysed. The exposure of interest was the use of GCs at baseline. As primary outcome we considered clinical and radiographic disease progression, assessed by the disease activity (DAS 28), function (HAQ DI) and structural joint damage (Ratingen erosion score). The baseline disease characteristics were compared using standard descriptive statistics. The effects of initial GC use on disease progression during follow up was estimated using linear mixed models with random slope and random intercept, adjusted for potential confounders.

Results: In total, 592 patients with early disease were available, with 4.3 years of follow-up (average). Of these, 363 were initially treated with glucocorticoids (GC patients) and 228 were not (no-GC patients). DAS-28 (4.6 vs. 4.3, $p = 0.01$) and the HAQ-DI (0.94 vs. 0.82, $p = 0.01$) were higher at baseline in GC patients, while other prognostic factors were balanced at baseline. Neither the change of DAS-28, of HAQ-DI, nor of the development of joint erosions differed between the two groups during follow up. Escalation of treatment employing biologics was documented in 18.0% of the no-GC patients and 27.3% of the GC patients ($p < 0.01$).

Conclusion:

In this cohort, patients with early RA initially treated with GCs had higher measures of disease activity at baseline in comparison to no-GC patients. Despite a similar course of the disease in GC versus non-GC patients, the higher escalation rate to biologic agents in GC patients may reflect a disease less responsive to therapy in these patients.

These data suggest that GC use as part of the initial therapeutic strategy in early RA may prevent a more severe course of the disease in patients with higher clinical disease measures at the start of therapy.

Key words: glucocorticoids, rheumatoid arthritis, disease progression, early disease

Significance & Innovation:

- GC use may have a beneficial role in patients with unfavourable prognostic factors.
  - Patients with initial GC treatment had more unfavourable prognostic factors than those without.
  - Early RA patients with and without initial GC use demonstrated similar clinical and radiographic development during follow-up.
- In our opinion, in the absence of contraindications, GCs should always be considered as bridging therapy in early disease, and used, in particular, if unfavourable prognostic factors are present.

Introduction:

Glucocorticoids (GC) have anti-inflammatory and disease-modifying properties in RA patients (1-3). GC treatment added to DMARD therapy is successful at low (<10 mg/day) (4-6) and at higher doses (7, 8). Higher doses of GCs lead to a more rapid short-term clinical improvement in comparison to patients not treated with GCs at all (7). In the COBRA-light study a reduced glucocorticoid dose was equally effective as higher GC doses employed in the classical COBRA regimen (9).

Whether the significantly better outcomes in clinical trials using combinations of synthetic DMARDs plus GCs versus DMARD monotherapy might be at least in part be due to the GC component (6-8) is under discussion. This hypothesis is supported by studies showing that adding GC to DMARD monotherapy(4, 5) is beneficial.

It is well known that long or even intermediate-term use of GCs can lead to adverse events (10). The EULAR task force, therefore, recommends that GCs should be tapered as rapidly as possible (11).

The primary objective of this study was to analyze whether initial corticosteroid therapy influences the course of early disease in RA patients. A secondary objective of this study was to compare baseline characteristics of early arthritis patients with or without initial GC use, possibly explaining the rheumatologist's decision to add GCs.

METHODS:

Study population and design

The Swiss Clinical Quality Management in rheumatoid arthritis (SCQM) is a RA national cohort study performed by office or hospital based rheumatologists, which has been described in detail elsewhere (12, 13). SCQM has obtained a Swiss-wide ethical approval to collect patient data and a broad consent to perform clinical research related to its aims. In this study, we restricted our analysis to patients with early RA. The analysis includes data collected between January 1998 and November 2011. Inclusion criteria for the analysis were a diagnosis of RA by a rheumatologist, and early disease, as defined as less than 367 days from the first symptoms (as reported by the patient). Patients treated with GCs, synthetic or biological DMARDs for more than 31 days before the first visit were excluded from the analysis. Exclusion criteria were missing 28 joint counts at baseline or the absence of follow-up visits, as published before (14, 15).

Exposure of interest

The primary objective of the study was to analyse whether initial GC therapy influences the course of the disease in early RA patients.

Outcome parameters

The primary endpoint was the change of DAS-28 scores. Secondary endpoints were changes in radiographic joint damage and patient centred outcomes. The patient centred outcome was assessed using the Stanford Health Assessment Questionnaire (HAQ DI) (16). Radiographic damage was analyzed on serial radiographs according to the number and the size of bone erosions. Erosions were measured prospectively using a validated scoring system (Ratingen score) (17), based on the amount of joint-surface destruction for each joint. The inter-observer agreement and test-retest reliability were high, as published (17).

To predict, at baseline, the GC use after 2 years, as a secondary endpoint, all RA patients were separated into two groups depending on the documented GC use after two years (defined as long-term use of GCs). The two groups were re-analyzed for differences in baseline characteristics.

Statistical analysis

The baseline disease characteristics of patients in the two groups were compared using standard descriptive statistics. Continuous variables were compared using a Student´s T-test, categorical variables with X^2 test. Curves showing changes in DAS-28 and HAQ DI scores over time were created using loess smoothing of the raw data. The effect of initial GC use on DAS-28 and HAQ DI scores was estimated using linear mixed models with random slope and random intercept, and adjusted for various baseline factors in a univariate fashion, as well as in a multivariate fashion considering baseline DAS-28 (or HAQ DI), Ratingen score and ESR. We also examined whether GC initiation was influenced by baseline parameters, ACR/EULAR classification score, rheumatoid factor, DAS-28, ACPA, ESR, age, gender or calendar year of inclusion, in a propensity score analysis using multiple logistic regression. A propensity score was then computed as the predicted log-odds of receiving GCs at baseline, and included as a univariate predictor in the linear mixed models described above. All statistical analyses were 2-sided at the 0.05 significance level. The analyses were performed using Graph pad Prism 5 software and the lme4 package in R.

Ethics approval

Ethics approval for the collection of patient data for the SCQM Cohort was given by the regional review boards. Informed consent was obtained from all patients before inclusion in the SCQM Cohort.

RESULTS:

Patients:

Of the 9´627 patients in the database, 756 patients had early RA with a symptom duration of less than 367 days. 609 patients of these had at least one follow-up in the database, and 592 patients in the database had valid 28 joint counts. The median follow-up for these 592 patients was 44 months (range 0 – 178), representing a total of 3'845 visits.

Baseline demographical data:

Patients were categorized into two groups: patients treated with GCs (GC patients, n=363) and not treated with GC (n=228, no-GC patients) at baseline. Analysis of the demographical data revealed no significant differences in age, gender, disease duration, and time of follow up between the two patient groups, as shown in Table 1. In 2 patients new treatment was initiated within the period of 31 days prior to baseline. Exclusion of these patients from did not influence data analysis (not shown). Disease activity was higher at the inclusion visit in GC patients. In detail, mean DAS-28 was 4.6 in GC patients vs. 4.3 in no-GC patients (p = 0.011). Similarly, the ESR was also higher in GC patients (mean 30.5 vs. 24.3mm/h, resp., p = 0.0013), whereas CRP (mean 23.7 GC vs. 15.8 no GC, p = 0.13), swollen (7.9 vs. 7.1, p = 0.09) and tender (8.0 vs. 7.6, p = 0.48) joint count, and erosion scores at disease onset showed no statistically significant differences. ACPA and rheumatoid factors also did not differ between the two patient groups. The average HAQ DI was higher in GC (0.94) than in no-GC patients (0.82, p = 0.0122, Table 1).

The average GC dose in the GC patients was 14.0mg/d (±9.28)at baseline (median 10mg/d). The range was from1.25mg/d to 60mg/d (Figure 1).

Clinical and radiographic progression:

Disease activity, patient reported outcome, and development of joint erosions were similar in both patient groups during follow up, as demonstrated by DAS-28, HAQ-DI, and erosion scores (~~Figure 1~~Figure 2). The time of follow up between the two patient groups did not differ (mean 171.2 months GC vs. 186.9 months no-GC, p = 0.0529).

To find out whether GCs were preferentially started in more severe cases of RA, we analyzed if GC initiation was associated with the baseline parameters (rheumatoid factor, DAS-28, ACPA, ESR, age, gender and calendar year) in a propensity score analysis using logistic regression (not shown). After adjusting for this propensity score, no statistically

significant difference in clinical activity (difference in DAS-28 0.04 on average, p = 0.67) or radiographic disease progression (erosion score 0.75 higher in GC patients, p = 0.29) was observed in patients with and without the use of GCs. The same was true for the patient oriented outcome (HAQ-DI 0.03 higher in GC patients, p = 0.47). The results were similar when using a propensity score from the best-fit model, which included only age and baseline ESR.

Drug survival of initial GCs and new initiation of GCs during follow up:

The drug survival of GCs after start at baseline was analyzed. GC treatment was stopped in 301 patients during follow up, after a median of 680 days. In parallel, GC treatment was initiated in 48 of the initial no-GC patients after an average of 662 days (~~Fig.~~Figure ~~2A~~3A). Thus, GC treatment was continued in 47.2% of the initial GC patients and started in 21.9% after 2 years of follow up of the initial no-GC patients (not statistically significant).

Conventional synthetic DMARD treatment:

Treatment with conventional synthetic DMARDs was initiated preferentially with methotrexate (MTX) in both treatment groups. MTX was a part of the initial therapeutic strategy in 75.5% of the GC patients and 66.9% of the no-GC patients (X^2 test: 4.492,1, p = 0.03, table 2). The average initial MTX doses were 14.4 and 14.1mg/week in the GC and no-GC patients respectively (data not shown). In parallel, the first therapeutic modification (independent of whether the MTX dose was modified in patients already treated with MTX or whether MTX was initiated) was more frequent in GC patients (23.4% in GC vs. 4.7% in no-GC patients, X^2 test: 38.32,1, p < 0.0001). There were no significant differences comparing GC and no-GC patients for the use of sulfasalazine, anti-malarials, and leflunomide (data not shown).

Escalation to biologics:

Escalation of treatment with biologic agents occurred in 18.0% of the no-GC patients after 909 days on average and in 27.3% of the GC patients after 754 days (X^2 Test for the number of patients requiring biologics: 6.96, p = 0.0097, time to first biologic p = 0.31, ~~Fig.~~Figure ~~2b~~3b).

Co-morbidities:

Analysis of the number and kind of co-morbidities in our cohort of early RA patients did not reveal differences between the two patient groups, neither at baseline, nor during follow up (table 3).

Predictors for GC use after 2 years

To explore which baseline parameters were associated with long-term GC treatment, we examined patients still on GC after 2 years (table 4). Patients with long-term GC use over 2 years had an increased HAQ DI of 1.05 at baseline, as compared to 0.86 in those not treated with GCs after 2 years ($p = 0.005$), but no other differences were found for the different demographical, serological, and parameters indicative of disease activity or joint destruction.

Discussion:

In this study, we analyzed the effect of initial GC treatment as an adjunct to DMARD therapy in a cohort of 592 RA patients with early disease. Patients treated with GCs had higher objective and subjective disease activity at the first visit, as measured by the DAS-28 and HAQ DI, respectively. These differences evened out during follow up.

These results may help to shed light on two frequently debated questions:

- Is the decision for initial treatment with GCs triggered by unfavourable prognostic factors?
- Is GC use from first clinical visit onwards in early RA necessary to modify the further course of the disease?

Is the decision for initial treatment with GCs triggered by unfavourable prognostic factors?

In our study, disease activity (ESR, DAS-28) was higher and functional limitations (HAQ DI) were more pronounced in patients initially treated with GCs than in those who were not. The most likely explanation is that rheumatologists tended to add concomitant GC preferentially to their patients with more severe RA, which is corroborated by the fact that these patients also received more frequently biologic anti-rheumatic agents during follow-up than non-GC users.

It is well known that long-term GC treatment is associated with many adverse events. As a consequence, rheumatologists try to taper and eventually stop GCs. The reasons for maintaining GC treatment for an extended period of time should be well founded and GCs should only be used because of a therapeutic necessity in the individual patient. In our study, 20 – 50% of the patients were still treated with GCs after two years (~~Fig.~~Figure ~~2~~ 3A). The HAQ DI at baseline was the only parameter significantly higher in patients on GCs after two years. The patient's individual perception of disease-associated limitations affecting functionality in daily life, thus, correlated with the use for GCs after two years.

Another explanation for initial use of GCs could be the application of predefined therapeutic concepts including the use of GCs in all early RA cases by individual rheumatologists or centers. However, we could not demonstrate an association between the initial use of GCs and individual rheumatologists or centers involved (data not shown), suggesting that GC use was no related to a strong physician bias as in a natural study.

Is the GC use from first clinical visit onwards in early RA necessary to modify the further course of the disease?

In view of the loss of the initial differences in disease activity during follow up, our data suggest -at first sight - that the initial use of GCs does not improve long-term results.

No differences between patients initially treated or not with GCs in radiographic progression, DAS-28 or HAQ DI could be found. However, biologic agents were more frequently initiated during follow up in GC- than in no-GC patients, most probably reflecting an initial clinical disease state less responsive to therapy in these patients. GC may only be necessary in patients with higher baseline DAS and HAQ-DI scores.

A considerable number of clinical studies (18) has demonstrated that more aggressive treatment may lead to better results (19). Increased baseline parameters such as ESR, high joint counts as part of the DAS-28 and HAQ DI are known to have a negative influence on the course of RA (20, 21) . These parameters were higher in the GC group (22) of our cohort, indicating a potential for more aggressive disease. Considering the equal course of disease in the two patient groups, GCs may actually have prevented a more severe course of the disease. In the EULAR guidelines recommend that “low-dose glucocorticoids” should ideally be considered ”as part of the initial treatment strategy” since addition of GCs to DMARD therapy as “bridging therapy” has been shown to have a similar effect as the addition of a TNF antagonist to MTX (11, 23-25). In view of the multitude of parameters involved, data derived from clinical cohorts are never unequivocal. Our analysis, however, may support the use of GC in early RA in patients with higher clinical disease measures such as higher DAS-28, ESR and HAQ-DI (high DAS-28, ESR, and HAQ-DI, (20, 21)). This conclusion is similar to the statement in the EULAR guidelines in Phase II for the therapeutic decision after the first DMARD has failed (11). These recommendations propose a second synthetical DMARDs in patients with favourable and a first biologic agents in those with unfavourable prognostic factors.

Health economic considerations:

The percentage of 27% GC- and 15% no-GC-patients requiring a step up of therapy to a biologic agent appeared rather low. A possible reason for this may have been the relatively early recruitment period of January 1998 and November 2011(median May 15th 2005) in our cohort. However, this rate is comparable to others published by Fiehn et al. in Germany for the time period 1997 – 2005 or, more recently, for the Dutch tREACH cohort (23, 26). Considering yearly costs of CHF 21´232,90 for a biologic agent (e.g. Adalimumab, Switzerland OTC price) and CHF 119,-- for 10 mg prednisolone (e.g. Spiricort, Switzerland OTC price), reduction of biologic agents by e.g. 5% would be equivalent to overall savings of CHF 94´265 (in 100 patients). Or, in other words, the costs would be equivalent if 178 early RA patients are treated continuously with prednisolone over one year and in one patient out of these 178 therapy is not escalated a biologic agent. These considerations are, as a matter of course, purely economic and do not take into account costs caused by therapy related side effects of either corticosteroids or biologics.

Limitation:

GCs are frequently associated with AEs. Assessment of AEs is certainly an issue for the analysis of cohort data. We have analysed the adverse event rate in both groups and found no differences between the two groups (data not shown). The relative risk for a comorbidity was 1.12 comparing GC and no GC patients. The leads to a number needed to harm (NNH) of 1960.1. However, the rate of AEs was very low and we think that underreporting of AEs is a major bias to this analysis.

The initial glucocorticoid doses employed in the GC patients varied from 1.25 to 60mg/d at onset of treatment. The improved effect of higher initial GC doses has been reviewed by Laan et al. (27). However, it cannot be derived from the database whether the physicians coded the GC dose initiated or, rather, the dose reached after initial tapering. Therefore, no conclusions can be drawn from our data on the initial GC dose used and its effect on the course of the disease.

Summary and conclusions:

Patients with initial GC treatment had more unfavourable prognostic factors than those without, implying a more aggressive evolution of their disease. However, early RA patients with and without initial GC use demonstrated similar clinical and radiographic evolution, suggesting that initial GC use may have had a beneficial role in these patients with unfavourable prognostic factors. In our opinion, in the absence of contraindications, GCs should ~~always~~ be considered as bridging therapy in early disease~~, and used,~~ in particular, if prognostic factors of severe disease are present.

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Tables, Figure legends:

Table 1: Patient baseline characteristics

GC use initiated at baseline	Present	Not present	P value
Number	363	228	-
Age (years, mean ± SD)	55.1 ± 14.8	51.3 ± 15.2	0.034
Gender (f/m)	257/106	172/56	0.214
Follow-up (months, mean ± SD)	51.4 ± 37.2	50.6 ± 39.1	0.80
Symptom durations (days, mean ± SD)	171.2 ± 98.5	186.9 ± 94.5	0.0529
SJC at onset (mean ± SD)	7.9 ±6.0	7.1 ± 5.9	0.088
TJC at onset (mean ± SD)	8.0 ± 6.8	7.6 ±6.6	0.48
DAS-28 at onset (mean ± SD)	4.6 ± 1.6	4.3 ± 1.6	0.011
RF pos. at onset (n, %*)	231, 63.6%	157, 68.9%	0.19
CCP pos. at onset (n, %*)	85, 62.0%	66, 65.3%	0.60
ESR at onset, mm/h (mean ± SD)	30.5 ± 25.3	24.3 ± 20.4	0.0013
CRP at onset, mg/l (mean ± SD)	23.7 ± 12.1	15.8 ± 11.5	0.13
Ratingen score at onset	8.9 ± 9.6	7.1 ± 8.4	0.0614
HAQ-DI at onset	0.94 ± 0.71	0.82 ± 0.65	0.0122
Initial GC dose (av. mg ± SD, range, median)	14.1 ± 9.8, 2.5-50, 10	0 ± 0, 0	-

f: female
GC: Glucocortioid
m: male
TJC: Tender joint count
SJC: Swollen joint count
RF: rheumatoid factor
CCP: antibodies to cyclic citrullinated peptides
CRP: C reactive protein
n.a. not applicable
LORA: Late onset rheumatoid arthritis (>60a)
YORA: Young onset rheumatoid arthritis (<60a)

- Calculated on patients with available data

Table 2: Percentage of patients on certain drug therapy (%)

		MTX	SSZ	Lef	HCQ
Initial therapeutic strategy	No-GC	66.9	10.5	6.8	6.0
	GC	75.5	12.0	4.6	9.8
1st modification of initial therapy	No-GC	4.7	6.0	5.5	6.9
	GC	23.4	7.2	11.0	6.3
2nd modification of initial therapy	No-GC	6.1	4.4	6.1	2.2
	GC	9.2	4.4	4.1	3.6
3rd modification of initial therapy	No-GC	5.3	0	1.8	1.3
	GC	4.4	0.6	5.2	1.9
4th modification of initial therapy	No-GC	1.3	0.4	1.3	0.9
	GC	1.3	0.6	2.2	0.8

No-GC: Patients initially treated with glucocorticoids
GC: Patients initially treated without glucocorticoids
MTX: Methotrexate
SSZ: Sulfasalazine
Lef: Leflunomide
HCQ: Hydroxychloroquine

Table 3: Comorbidities:

	GC	no-GC
Total	n = 92	n = 51
Allergical	n = 11	n = 5
Cardiological	n = 5	n = 2
Dermatological	n = 18	n = 7
Gastrointestinal	n = 24	n = 16
General	n = 2	n = 4
Hematological	n = 1	n = 3
Hepatical	n = 1	-
Ears, nose, through	n = 2	n = 2
Infectious	n = 8	n = 4
Musculosceletal	n = 2	-
Neoplasia	n = 1	n = 3
Nephrological	n =1	-
Nephrological	-	n = 1
Neuropsychiatric	n = 8	n = 1
Not defined	n = 3	n = 1
Ophthalmologic	n = 1	-
Pulmonary	n = 4	n = 2

Table 4: Patient characteristics at baseline depending on the GC use after two years

GC used after 2 years	still on GC	no-GC	P value
Number	153	439	-
Age (years, mean ± SD)	54.6 ± 15.1	53.3 ± 15.1	0.37
Gender (f/m)	112/41	317/122	0.06
Follow-up (months, mean ± SD)	63.7 ± 36.5	46.8 ± 37.5	<0.0001
Disease durations (days, mean ± SD)	181.2 ± 99.7	175.8 ± 96.4	0.56
SJC at onset (mean ± SD)	7.8 ± 6.1	7.5 ± 5.9	0.66
TJC at onset (mean ± SD)	8.3 ± 7.2	7.7 ± 6.5	0.32
DAS-28 at onset (mean ± SD)	4.6 ± 1.6	4.5 ± 1.5	0.30
RF pos. at onset (n, %*)	107, 69.9 %	281, 64.0%	0.18
CCP pos. at onset (n, %*)	35, 62.5%	116, 63.4%	0.90
ESR at onset, mm/h (mean ± SD)	31.2 ± 24.8	27.1 ± 23.3	0.08
CRP at onset, mg/l (mean ± SD)	27.0 ± 9.1	19.3 ± 12.6	0.45
Ratingen score at onset	8.1 ± 8.6	8.4 ± 8.6	0.74
HAQ-DI at onset	1.05 ± 0.73	0.86 ± 0.67	0.005

f: female
GC: Glucocorticoids
m: male
TJC: Tender joint count
SJC: Swollen joint count
RF: rheumatoid factor
CCP: antibodies to cyclic citrullinated peptides
CRP: C reactive protein
n.a. not applicable
LORA: Late onset rheumatoid arthritis (>60a)
YORA: Young onset rheumatoid arthritis (<60a)
* Calculated on patients with available data

Figure 1: Average GC doses. The average GC doses are demonstrated depending on the number of patients initiated on the respected dose

~~Figure 1~~**Figure 2: DAS-28, HAQ scores and radiographic progression over time.** Patient groups were analyzed separately for initial GC (dotted grey line, GC patients) and no initial GC use (solid black line, no-GC patients). Loess smoothed time-courses of DAS-28 (A), Ratingen (B), and (C) HAQ DI scores are depicted per group over 60 months of follow-up.

~~Figure 2~~**Figure 3. Time to stop/start glucocorticoids and time to start the first biologic DMARD.** (A) The time to stop glucocorticoids (black line) and the time to start glucocorticoids (grey line) in patients initiated with GC (black line) and patients initiated without GCs (grey line). The time was assessed in days from the first documented therapy for RA in our cohort within the SCQM registry. Patients are presented as percentage of either group. (B) The time to initiation of the first biologic DMARD was shown in days after the first visit in patients initiated without glucocorticoids (black line) and patients initiated without GCs (grey line). Data was shown as percentage per patient group. The time to biologic is demonstrated as days after the first visit.